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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,117	11/18/2003	Jing Li	006539.00051	6377

22907 7590 02/07/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
02/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,117	LI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 135-144* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 135-144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, and 135-143 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 10/31/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Priority

1. This instant application claims priority to provisional applications 60/427,202 (filed 11/19/2002) and 60/434,434 (filed 12-19-2002). However, the subject matter of the examined claims (claims 1-3, methods using SPHK1 gene copy number) was not disclosed in the '202 provisional application, thus the claims do not have priority to the '202 provisional application. The subject matter of the examined claims is disclosed in the '434 provisional application, thus the claims have priority to the 60/434,434 provisional application (filed 12-19-2002).

Withdrawn Claim Objection

The objection to Claim 139, as set forth in the previous Office Action, Is **WITHDRAWN** in light of the amendment to claim 139.

Maintained Claim Rejections - 35 USC § 112 1st¶ - Scope of Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 135-138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A screening method comprising determining sphingosine kinase 1 (SPHK1) human gene copy number, wherein said sphingosine kinase 1 (SPHK1) human gene encodes an mRNA comprising SEQ ID NO: 3, in a test sample, and comparing the test sample copy number to data for a control gene copy number obtained from a control sample of the same tissue type as the test sample,

does not reasonably provide enablement for a method comprising analysis of the broadly claimed 'sphingosine kinase 1 (SPHK1) human gene copy number'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The rejected claims are drawn to methods for screening for a cancer comprising determining SPHK1 human gene copy number, and as such encompass determining

the copy number of any 'sphingosine kinase 1 (SPHK1) human gene'.

The nature of the claims requires knowledge of a correlation between copy number of the broadly claimed 'sphingosine kinase 1 (SPHK1) human gene' and the suggestion of the presence of a precancerous lesion or a cancer.

Direction provided by the specification and working example

The specification of the instant application asserts that it has been determined that SPHK1 is amplified and/or overexpressed in human cancers (p.66). The specification asserts that human chromosome region 17q25 is one of the most frequently amplified regions in human cancer, and that in the process of characterizing a 17q25.2 amplicon SPHK1 was found amplified in several tumor samples (p.67). The specification teaches that amplification of SPHK1 was determined by microarray analysis (p.67).

The specification teaches several definitions relevant to the breadth of the rejected claims. The specification teaches that 'cancer' includes the presence of cells possessing characteristics typical of cancer-causing cells, and specifically includes leukemic cells. The specification further defines a 'gene' as a region on genome capable of being transcribed to an RNA that has a regulatory or catalytic function or encodes a protein and encompasses spice variants, allelic variants, and transcripts arising from alternative promoter or poly-adenylation sites (p.32). The specification further defines SPHK1 as encompassing polymorphic variants, alleles, mutants, and interspecies homologs with various, not clearly defined, levels of homology and identity to GenBank NM_021972 (nucleic acid sequence), Genbank NP_069907.2 (polypeptide

sequence), and SEQ ID NO: 1, 2, and 3 (nucleic acid and polypeptide sequences). (p.66).

Because the claimed method comprises determining gene amplification, it is relevant to point out that the instant specification broadly defines the term 'amplification' as encompassing amplification, duplication, and multiplication, of a gene yielding about 3.0 fold or more copies. However, an SPHK1 gene copy number of less than 3.0 fold can still be considered an amplification (p.34). The specification further defines an 'amplicon' as the amplification product of a gene, indicating that the term includes partially amplified SPHK1 (p.35).

Thus given the definitions provided by the specification, the claimed methods encompass detecting amplification of any portion of a gene sequence with even a small degree of sequence similarity to the any variant of an SPHK1 gene or cDNA sequence (where it is noted that the provided SEQ ID NO: 1 and 2 are cDNA sequences, and not genomic sequences that encode the SPHK1 transcript). For example, a polymorphic variant of an SPHK1 gene which contains a three nucleotide repeat insertion would be a gene amplification.

The specification provides an example of the analysis of SPHK1 gene amplification in cells from human tumors (Examples I, II, and III, pages 111-114). The Examples of the specification teach that DNA microarray based CGH was used to survey the genome for gene amplification, and it was determined that SPHK1 is frequently amplified in tumor tissues and cell lines. The specification teaches analysis of SPHK1 gene copy number in breast, ovarian, colon, bladder, and lung tumors (Table

1). The specification teaches that SPHK1 gene amplification was detected from 3% to 33% of the time. For example, amplification was detected in 1 out of 30 lung tumor samples. In the case of bladder cancer, amplification was found in 3 out of 9 samples (33%).

The specification does not provide the sequence of the microarray probes used to determined SPHK1 gene amplification, nor the method in which gene amplification was determined for the data in Table 1, nor the nature of the amplicon (e.g. the portion of the SPHK1 gene that is amplified in a tumor sample).

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection and quantitation of a particular nucleic acid sequence in a sample is high, the level of unpredictability in associating any particular gene or copy number of a gene with a phenotype is even higher, where in the instant case the unpredictability is intensified by the breadth of the claims with regard to the SPHK1 gene and control copy number from any 'corresponding tissue'. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Though the prior art teaches a role of sphingosine kinase in the development of cancer phenotypes (Xia et al, 2000, as cited in the IDS), the prior art does not teach the reliable association of amplification of any SPHK1 gene as broadly claimed and defined in the instant specification with the suggestion of cancer.

And while the specification teaches the breadth of the term 'SPHK1 gene', the examples presented in the specification do not address the different sequences

encompassed by the claims. For example while the claims encompass analysis of any polymorphic variant, the specification does not teach the analysis of any variants of the SPHK1 gene. The art teaches a variety of polymorphisms in the SPHK1 gene including at least 27 SNPs (GeneCard for protein-coding SPHK1, pages 7-8). Notably, one SNP (rs3744040; CAG to TAG) creates a Gln to STOP codon change in the protein-coding region. Based on the prior art of Xia et al (which teaches a role of over expression of the sphingosine kinase in cancer development) coupled with the teachings of the instant application (which asserts that gene amplification leads to overexpression (Table 2)), it is unpredictable as to whether or not amplification of a gene containing, for example, the rs3744040 SNP (coding for a truncated amino acid sequence), or any other SNP, would be indicative of cancer.

Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). It is thus not established by the teachings provided in the instant specification whether or not a measure of copy number of any SPHK1 gene, as broadly defined in the specification, can reliably suggest the presence of cancer.

Quantity of experimentation required

A large amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include examining any possible variant of the SPHK1 gene as broadly defined in the specification to determine which of the possible myriad of sequences are suitable for screening for the cancers recited in the claims. Application of the method to the specifically recited forms of cancer would require validation every possible gene variant to establish that such 'SPHK1 human gene' copy number suggests the presence of cancer'. Such experimentation would involve the analysis of an enormous number of nucleic acid sequences.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks

Applicant has traversed the rejection of claims under 35 USC 112 1st¶ as lacking enablement. Applicants' arguments have been fully considered but are not found to be sufficient to put the claims in condition for allowance.

Applicants argue (p.5 of Remarks) that the plain language of independent claim 1 requires determining the copy number of human SPHK1 gene, and that the definition of

SPHK1 from page 66 of the specification as relied upon by the Examiner is overly broad and it is not proper the import this overly broad definition from the specification into a claim. These arguments has been considered but is not found to be persuasive. Initially it is noted that MPEP 2111 addresses proper claim interpretation, specifying:

> The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1).

In the instant case of the rejected claims, the Examiner must consider the very broad definition of SPHK1 as provided by the Applicants' themselves in constructing the breadth of the claimed methods. And while the Examiner agrees that 'there is no protein or polypeptide recited in claim 1', and that claim 1 specifically recites 'the SPHK! human gene' (p.6 or Remarks), the examiner maintains that the term SPHK1 encompasses a wide variety of nucleic acid sequences, and specifically contemplated by the definition of the Applicants (p.66 of the specification), where the breadth of nucleic acids encompassed by the methods is not enabled by the particular examples and teachings of the specification in combination with the knowledge of the skilled artisan. The Examiner maintains the claims are properly rejected for lack of enablement when given their broadest reasonable interpretation in light of the teachings of the specification.

The rejection is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 112 1st – Written Description

Claims 1, 2, and 135-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> Applicant is referred to the guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for diagnosing cancer comprising determining SPHK1 human gene copy number. The rejected claims provide no structural limitation regarding what is encompassed by the term 'sphingosine kinase 1 (SPHK1) human gene'.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to screening for cancer by determining SPHK1 human gene copy number in a test sample. The specification teaches a broad definition of 'gene' as a region on the genome that is capable of being transcribed to an RNA (p.32), and encompasses all SPHK1 transcripts that may be found including splice variants, allelic variants, and transcripts that occur because of alternative promoter sites or alternative poly-adenylation sites (p.33). The specification further teaches a broad definition of 'SPHK1', indicating that the term 'SPHK1' may include polymorphic variants, alleles, mutants, and interspecies homologs that have (i) for example as little as 60% nucleotide identity to GenBank NM_021972, (ii) as little as

65% amino acid homology to GenBank NP_068807.2, (iii) for example as little as 60% homology with the nucleotide sequence of SEQ ID NO: 1, or (iv) 'substantial sequence homology with the encoded amino acid (for example, SEQ ID NO: 2)' with no clear definition of 'substantial sequence homology' (p.66). Additionally, the specification teaches a definition of 'amplicon' as an amplification product that may include a part of SPHK1 (p.35). Thus the rejected claims encompass analysis of any portion of any variant of any SPHK1 human gene, which may include gene sequences very different from the disclosed SEQ ID NO: 1, and genes that encode polypeptides very different from the disclosed SEQ ID NO: 2, including sequences containing any polymorphisms (e.g. any insertion, deletion, or repeat at any location within the gene) and mutations not taught by the instant specification and not yet known in the art.

In analyzing whether the written description requirement is met for genus claims for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Nucleic acids of such a large genus as encompassed by the rejected claims have not been taught by the specification. The specification of the instant application discloses only SEQ ID NO: 1 (a human SPHK1 cDNA sequence), SEQ ID NO: 3 (the protein coding portion of SEQ ID NO: 1), and SEQ ID NO: 2 (the amino acid sequence encoded by SEQ ID NO: 3).

In analyzing whether the written description requirement is met for genus claims it is next determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and

functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the sequence of the human SPHK1 gene (SEQ ID NO: 1 and 3) and the encoded amino acid sequence (SEQ ID NO: 2). The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of cancer based on amplification of the non-disclosed gene.

> Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:
>
> > It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, with the exception of a method for diagnosing cancer comprising determining the copy number of a gene consisting of the particular sequences disclosed in the specification, one of skill in the art cannot envision the detailed chemical structure of the encompassed polynucleotides (i.e. any SPHK1 genes the amplification of which is suggestive of cancer), regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that any genetic variants or fragment of the gene is part of the claimed invention and a qualitative description of the nature of the variant (e.g. amplification is associated with cancer).

In conclusion, the limited information provided regarding the association of SPHK1 (including disclosure only of SEQ ID NO: 1, 2, and 3) gene amplification with cancer is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of methods comprising the analysis of any gene variants or fragments besides those particularly disclosed in the specification at the time the application was filed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ as lacking adequate written description of the claimed subject matter. Applicants' contend (p.5-7 of Remarks) that the Examiner has not set forth express findings of fact to support a prima facie case of lack of written description as required by MPEP 2163.04. This argument is not found to be persuasive. As addressed in the earlier Response to Remarks of this Office Action, and detailed in the rejection, at issue in the case of the instant claims is breadth of the term 'SPHK1' required by the rejected claims. And while Applicants point out (p.6-7 of Remarks) that a specification adequately describes a genus to the skilled artisan if it permits the artisan to recognize members of the genus, and that the naturally occurring SPHK1 gene was well known in the art at the time of the invention, the issue of what was known in the art is opposed by the definition provided by Applicants (p.66 of the specification) of the nucleic acid sequences encompassed by

the term 'SPHK1'. The breadth of the claims thus encompasses for example, the analysis of variant nucleic acid sequences of SPHK1 that have as little as 60% sequence identity with what one of skill in the art would recognize as the SPHK1 of GenBank NM_021972. Thus the line between what one of skill in the art would recognize as the SPHK1 gene sequence, and what the specification particularly teaches is encompassed by 'SPHK1', as used in a method to screen for a cancer, is not limited to what Applicants argue is 'well known in the art' and 'does not require a structural recitation in either the specification or in the claims'.

The rejection as set forth is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 102

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Michelland et al (1999).

Michelland et al teaches the comparative genomic hybridization analysis of lung cancer cells as compared to non-cancerous tissue.

Regarding claim 1, the reference teaches CGH analysis of DNA extracted from lung tumors (p.22 – Tumor samples; p.23 – DNA extraction, labeling and in situ hybridization; Digital analysis). The reference specifically teaches the analysis of chromosomal gain at chromosome 17q (p.23 – High-grade NE lung tumors, NSCLC; Tables 1, 3, and 4), a region which encompasses the human SPHK1 gene (see for example Figure 1, which indicates gain of the region including SPHK1 gene in at least 9 tumor samples). Thus the analysis of tumor DNA by CGH is determining SPHK1 gene

copy number in a sample from a region suspected to be cancerous and generating data for a test gene copy number (p.23 – Digital image analysis), relevant to part (a) of claim 1. Relevant to part (b) of claim 1, the reference also teaches (p.23 – DNA extraction, labeling and in situ hybridization, Digital image analysis) that the CGH analysis included the simultaneous analysis of labeled DNA from tumor and normal tissue by hybridization to normal metaphase spreads. Because a normal tissue has two copies of any given chromosomal locus (i.e. diploidy) the analysis results in a comparison of test and control gene copy numbers, where the control gene copy number is two, and such a control gene copy number represents the SPHK1 human gene copy number of corresponding normal, cancer-free human lung tissue (i.e. normal cancer-free human lung tissue has two copies of the SPHK1 gene). The reference further teaches that amplification of the 17q region (which contains the SPHK1 gene) is a chromosomal amplification that suggests the presence of cancer (e.g. Table 3 and p.28, right col, last paragraph).

Regarding claim 2, the reference teaches the use of normal DNA as a control, and hybridization to normal metaphase spreads (p.51 – CGH). Thus the comparison to the control is a comparison to a normal diploid sample in which the copy number of the 17q region is two copies per cell.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by the teachings of Michelland et al. Applicants argue (p.8 of Remarks) that the examiner's reasoning in applying the 17q teachings of Michelland et al to the instant claims that require determining SPHK1 gene copy number is a reasoning in which the

teaching of a genus (i.e. amplification of genes in the 17q region) anticipates a species (amplification of SPHK1). This argument has been fully and carefully considered but is not found to be persuasive.

Applicants have presented the argument (p.8 of Remarks) that the claims of the instant specification are drawn to a species of invention requiring the analysis of the SPHK1 gene copy number, whereas the cited prior art is a genus where a larger genomic portion (i.e. the 17q region) is analyzed. In the instant case the teachings of Michelland et al drawn to the 17q analysis, and specifically the amplification of the 17q region as indicative of cancer, is inherently an anlysis of the SPHK1 gene, because the SPHK1 gene is a portion of the analyzed chromosomal region. As such, the analysis of Michelland et al is determining SPHK1 gene copy number becasue the SPHK1 gene is one of the genes in the locus analyzed by Michelland et al. The instant specification notes (page 67) that human chromosome region 17q25 is one of the most frequently amplified regions in human cancers, and more than one gene, including SPHK1, is located in this region.

While Applicants argue that the 'genus' of Michelland does not anticipate the 'species' of the instantly claimed invention, the application of the Michelland et al reference to the rejected claims is more accurately described as an issue of 'comprising' language as opposed to an issue of genus versus species. In the instant case the claims are drawn to methods 'comprising' (i.e. open to the inclusion of additional, unrecited elements or method steps (see MPEP 2111.03)), where an analysis of the amplification of the 17q region is a method comprising the analysis of the copy number

of a sphingosine kinase (SPHK1) gene. The instant claims broadly require 'determining SPHK1 human gene copy number', but do not set forth any specific or particularly limiting method steps that would serve to differentiate the claimed methods from the teachings of the prior art.

In the instant case, applicants may circumvent the rejection based on the cited prior art of Michelland et al by amending the claims such that the claimed method requires analysis only of the SPHK1 gene, or the correlation of amplification of only the SPHK1 gene with the presence of cancer. Alternatively, Applicants may circumvent the rejection under 35 USC 102 based on the cited prior art of Michelland et al by removing the recited element of lung cancer from the listing of cancers for which the claimed method is a screen.

The rejection as set forth is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 103
Maintained in part as the rejection applies to claims 135-138

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michelland et al (1999).

Michelland et al teaches CGH analysis of DNA extracted from lung tumors (p.22

– Tumor samples; p.23 – DNA extraction, labeling and in situ hybridization; Digital analysis). The reference specifically teaches the analysis of chromosomal gain at chromosome 17q (p.23 – High-grade NE lung tumors, NSCLC; Tables 1, 3, and 4), a region which encompasses the human SPHK1 gene (see for example Figure 1, which indicates gain of the region including SPHK1 gene in at least 9 tumor samples). Thus the analysis of tumor DNA by CGH is determining SPHK1 gene copy number in a sample from a region suspected to be cancerous and generating data for a test gene copy number (p.23 – Digital image analysis), relevant to part (a) of claims 1 and 139. Relevant to part (b) of claims 1 and 139, the reference also teaches (p.23 – DNA extraction, labeling and in situ hybridization, Digital image analysis) that the CGH analysis included the simultaneous analysis of labeled DNA from tumor and normal tissue by hybridization to normal metaphase spreads. Relevant to part (b) of claim 1, because a normal tissue has two copies of any given chromosomal locus (i.e. diploidy) the analysis results in a comparison of test and control gene copy numbers, where the control gene copy number is two, and such a control gene copy number represents the SPHK1 human gene copy number of corresponding normal, cancer-free human lung tissue (i.e. normal cancer-free human lung tissue has two copies of the SPHK1 gene). The reference further teaches that amplification of the 17q region (which contains the SPHK1 gene) is a chromosomal amplification that suggests the presence of cancer (e.g. Table 3 and p.28, right col., last paragraph). Thus Michelland et al teaches all of the limitations of claim 1, from which claims 135-138 depend.

Michelland et al does not particularly teach detectable amplification of specifically

at least three-fold, four-fold, five-fold, or ten-fold, as required by claims 135-138, respectively.

However, Micehlland et al does teach, when comparing hybridization of a control with a sample, that over-representation was indicative of a high-level amplification (amplification site) when the ratio exceeded 2.0' (p.23, right col., lns.12-19). Thus based on the express teachings of detection of amplification in excess of two-fold amplification (i.e. a ratio that exceeds 2.0), modification to the methods specifically taught in Michelland et al as required by the rejected claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Because Michelland et al provides teachings as to the amplification of the chromosome 17q, including the portion of 17q that comprises the SPHK1 gene, in the development of lung cancer (as provided in Figure 1), it would be obvious for the skilled artisan to consider any amplification of the 17q region, including amplifications of at least three-fold, four-fold, five-fold, or ten-fold as, as required by the claims where each claimed fold amplification is encompassed by the amplification ratio that exceeds 2.0 as taught by Michelland, as suggestive of the presence of cancer. One would have been motivated to include higher levels of 17q amplification as a determinant of the presence of cancer based on the teachings of Michelland et al that amplification of 17q, including high-level amplification, is indicative of cancer, thus providing a greater flexibility in application of the methods of Michelland et al in the detection of cancer. The skilled artisan would have a reasonable expectation of success based on the express teachings Michelland et al that amplification of 17q is indicative of cancer.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious in view of the teachings of Michelland et al. Applicants have argued that the rejection does not provide a required elements (i.e.: teaching, suggestion, motivation, and reasonable expectation of success) to establish a prima facie case of obviousness in light of the teachings of Michelland et al. Initially it is noted that MPEP 2141 provides guidelines for determining obviousness in light of the recent decision by the Supreme Court in KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. ___, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way. KSR, 550 U.S. at ___, 82 USPQ2d at 1391. Thus it is noted that the Supreme Court ruling for KSR (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching suggestion, or motivation is required to support a finding of obviousness. See Ex parte Smith (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007). The Examiner maintains that the rejected claims, broadly drawn to detecting particular fold-amplifications of the SPHK1 gene, are obvious to the skilled artisan in light of the teachings of Michelland.

With regard to Applicants' arguments concerning the reasonable expectation of success in the obviousness of the claimed method in view of the teachings of Michelland et al, the Examiner maintains that, as set forth in the rejection, the skilled artisan would have a reasonable expectation of success based on the express teachings Michelland et al that amplification of 17q, which comprises SPHK1, is

indicative of cancer.

Applicants have further traversed the rejection of claims as obvious in view of the teachings of Michelland et al arguing that 'that which may be inherent is not necessarily known'. With regard to the use of an inherent property of the sequence of an mRNA encoded by the SPHK1 gene (i.e. the requirement of SEQ ID NO: 3 in claims 139-144), it is noted that the portion of the rejection as set forth in the previous Office Action drawn to the obviousness of claims 139-144 in light of the teachings of Michelland et al is **WITHDRAWN.** Claims 139-144 are rejected in a new obviousness rejection as set forth later in this Office Action.

The rejection as set forth is **MAINTAINED.**

New Claims Rejections - 35 USC § 103

Claims 139-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michelland et al (1999), as applied to claims 135-138 above, in view of Meledez et al (2000) as evidenced by the provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al.

The teachings of Michelland et al are applied to claims 139-144 as they were previously applied to claims 135-138.

Relevant to claims 139 and 140, Michelland et al teaches determining in a test sample SPHK1 gene copy number, and comparing the test gene copy number to data for a control gene copy number, wherein the control gene copy number is two copies per cell, wherein gene amplification is indicative of cancer.

Michelland et al does not specifically teach an SPHK1 gene that encodes an mRNA comprising SEQ ID NO: 3 (as required by part (a) of claim 139), a control gene copy number obtained from a control sample of a same tissue type as the test sample, (as required by part (b) of claim 139), or detectable amplification of specifically at least three-fold, four-fold, five-fold, or ten-fold (as required by claims 141-144, respectively).

However, such additions to the methods of the express teachings of Michelland et al would have been obvious to one of ordinary skill in the art at the time the invention was made.

Regarding the limitations of part (a) of claim 139, Melendez et al teaches an analysis of the human SPHK1 gene indicating that it is located at chromosome locus 17q25.2 and encodes an mRNA comprising the sequence of SEQ ID NO: 3 (p.23 – huSPHK1 cDNA and peptide sequences, evolutionary comparison, genomic localization; Figure 1; and provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al.). Thus it would have been obvious to the skilled artisan to perform the method of Michelland et al for the analysis of the 17q locus comprising the SPHK1 gene encoding an mRNA comprising SEQ ID NO: 3, where the genomic location and sequence of the mRNA are specifically taught by Melendez et al. One would have been motivated to include the particularly required SPHK1 gene based on the teachings of Melendez et al concerning the genomic localization of the SPHK1 gene and the sequence of its encoded mRNA, and the teachings of Michelland et al that the 17q locus is amplified in cancer.

Regarding the limitation of part (b) of claim 139 that the control gene copy number is obtained from a control sample of a same tissue type as the test sample, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any known diploid tissue sample in a CGH study to provide a control gene copy number of two-copies per cell, including a control sample of the same tissue type. One would have been motivated to use the same tissue type in order to provide alternative techniques that would provide predictable results.

Regarding the limitations of claims 141-144, as discussed in the rejection above, Micehlland et al teaches that when comparing hybridization of a control with a sample, over-representation was indicative of a high-level amplification (amplification site) when the ratio exceeded 2.0' (p.23, right col., lns.12-19). Thus based on the express teachings of detection of amplification in excess of two-fold amplification (i.e. a ratio that exceeds 2.0), modification to the methods specifically taught in Michelland et al as required by claims 141-144 would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Because Michelland et al provides teachings as to the amplification of the chromosome 17q, including the portion of 17q that comprises the SPHK1 gene, in the development of lung cancer (as provided in Figure 1), it would be obvious for the skilled artisan to consider any amplification of the 17q region, including amplifications of at least three-fold, four-fold, five-fold, or ten-fold as, as required by the claims where each claimed fold amplification is encompassed by the amplification ratio that exceeds 2.0 as taught by Michelland, as suggestive of the presence of cancer. One would have been motivated to include higher levels of 17q

amplification as a determinant of the presence of cancer based on the teachings of Michelland et al that amplification of 17q, including high-level amplification, is indicative of cancer, thus providing a greater flexibility in application of the methods of Michelland et al in the detection of cancer. The skilled artisan would have a reasonable expectation of success based on the express teachings Michelland et al that amplification of 17q is indicative of cancer.

Response to Remarks

Though the above rejection based on the teachings of Michelland et al in view of Meledez et al as evidenced by the provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al is a new rejection, it is relevant to address Applicants' arguments on page 9 of the Remarks. The newly presented rejection incorporates the specific teachings of Melendez et al that the SPHK1 gene at locus 17q25.2 encodes an mRNA comprising SEQ ID NO: 3. As such, the rejection is not based on the inherent characteristic of the SPHK1 gene as encoding SEQ ID NO: 3, but is based on the particular teachings of the required sequence in the prior art.

Conclusion

5. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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2/3/2008